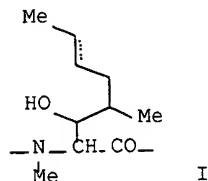


L35 ANSWER 108 OF 272 HCAPLUS COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 1998:674828 HCAPLUS Full-text  
DOCUMENT NUMBER: 129:343716  
TITLE: Method for phosphorylation of cyclosporins  
INVENTOR(S): Oki, Tadaki; Imano, Kiyotaka; Seto, Takashi; Ueda,  
Toshihiro  
PATENT ASSIGNEE(S): Nippon Shinyaku Co., Ltd., Japan  
SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.

DOCUMENT TYPE: CODEN: JKXXAF  
 LANGUAGE: Patent  
 FAMILY ACC. NUM. COUNT: 1 Japanese  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 10279596	A2	19981020	JP 1997-88311	19970407
PRIORITY APPLN. INFO.:			JP 1997-88311	19970407
OTHER SOURCE(S):	CASREACT 129:343716			
GI				



AB The alc. hydroxy group in the side chain (I) of cyclosporins is phosphorylated by activation of the hydroxy group with a base to the alkoxide and then reaction with a phosphorylating agent to give cyclosporin phosphate esters. The base capable of activating the alc. hydroxy group is Grignard reagent, alkali metal amide, and alkyllithium. Also claimed is an immunosuppressant containing cyclosporin phosphate esters. This process provides water-soluble cyclosporin phosphate esters, in particular cyclosporin A phosphate ester. Thus, 2.5 g cyclosporin A was dissolved in THF, treated with a 2M THF solution of Me<sub>3</sub>COMgCl (12.5 mL) at room temperature, and stirred for 15 min, followed by adding 1.34 mL adding di-Me chlorophosphate, (MeO)<sub>2</sub>P(:O)Cl, and the resulting mixture was stirred for 4 h to give cyclosporin A dimethylphosphate ester. The latter ester (100 mg) was dissolved in MeCN and treated with 220 µL thioanisole, 200 µL chlorotrimethylsilane, and 130 mg LiI under ice-cooling, and the resulting mixture was stirred at 0° for 25 h and treated with MeOH to give, after reversed phase chromatog. (LiChroprep RP-18), 71.8% cyclosporin A phosphate ester.

IT 215385-30-1P

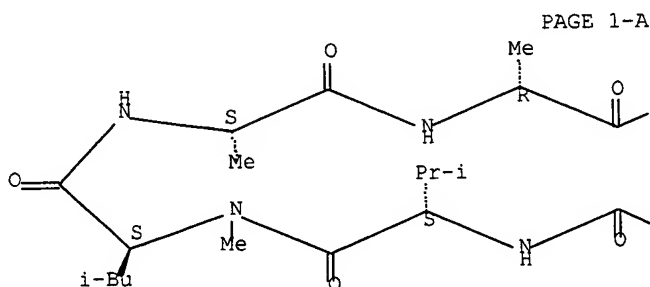
RL: RCT (Reactant); SPN (Synthetic preparation); PREP  
 (Preparation); RACT (Reactant or reagent)

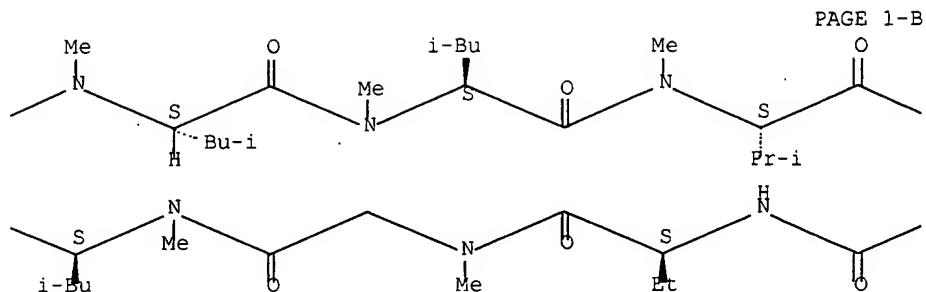
(method for phosphorylation of cyclosporins and preparation of cyclosporin phosphate esters for immunosuppressants)

RN 215385-30-1 HCAPLUS

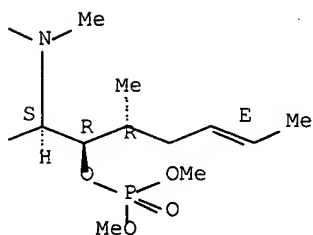
CN Cyclosporin A, dimethyl phosphate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.  
 Double bond geometry as shown.





PAGE 1-C



IT 173946-64-0P 174062-41-0P 215385-29-8P,

Cyclosporin A methylphosphate ester

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(method for phosphorylation of cyclosporins and preparation of cyclosporin phosphate esters for immunosuppressants)

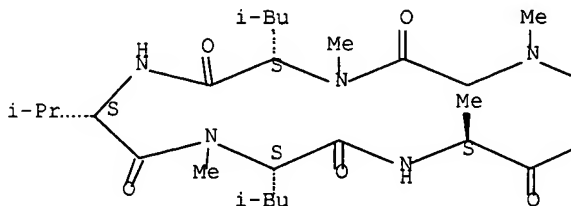
RN 173946-64-0 HCAPLUS

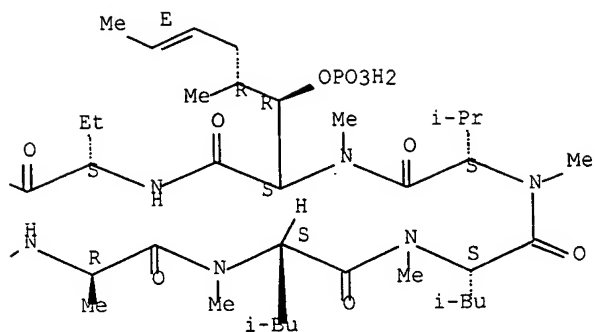
CN Cyclosporin A, dihydrogen phosphate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

Double bond geometry as shown.

PAGE 1-A



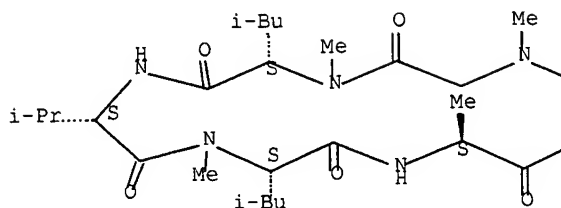


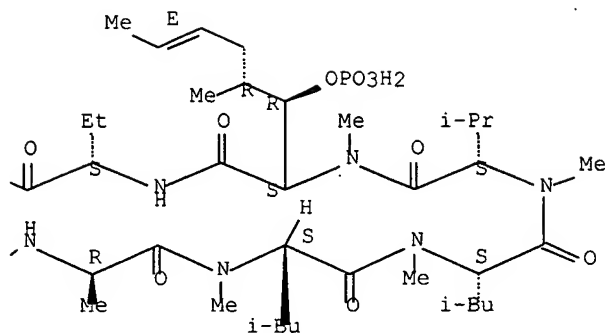
RN 174062-41-0 HCAPLUS

CN Cyclosporin A, dihydrogen phosphate (ester), disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).  
Double bond geometry as shown.

●2 Na





RN 215385-29-8 HCAPLUS

CN Cyclosporin A, methyl hydrogen phosphate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as shown.

